AUTOREGULATION OF CEREBRAL CIRCULATION

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Abstract: *Autoregulation of cerebral circulation is the mechanism by which the cerebral blood flow (CBF) is maintained constant between large limits of arterial pressure. Autoregulation appears only between certain pressure limits. The specialized literature presents 2 possible mechanisms of autoregulation: myogenic reaction and metabolic regulation. Sympathetic nervous system stimulation and the antagonism of renin-angiotensin system modulate CBF autoregulation, switching the curve to higher or smaller values of arterial pressure. Cerebral autoregulation is dependent on intracranial pressure as well on venous pressure. This paper is a review of the main mechanisms involved in cerebral autoregulation, its limits in hypertension, of the morphological changes in cerebral arteries and its assessment.*

Keywords: *cerebral autoregulation, mechanism, evaluation*

Rezumat: *Autoreglarea circulaţiei cerebrale este mecanismul prin care se menţine debitul sanguin cerebral (DSC) constant între limite largi ale presiunii arteriale. Autoreglarea apare numai între anumite limite de presiune. În literatură sunt prezentate 2 mecanisme posibile pentru autoreglare: reacţia miogenică şi reglarea metabolică. Stimularea sistemului nervos simpatic şi antagonismul sistemului renină-angiotensină modulează autoreglarea DSC, schimbând întreaga curbă spre valori ale presiunii arteriale mai mari sau, respectiv, mai mici. Autoreglarea cerebrală este dependentă de presiunea intracraniană, presiunea venoasă cerebrală. Această lucrare este o trecere în revistă a principalelor mecanisme implicate în autoreglarea cerebrală, a limitelor acesteia în hipertensiunea arterială, a schimbărilor morfologice în arterele cerebrale, precum şi a evaluării autoreglării cerebrale la om.*

Cuvinte cheie: *autoreglarea cerebrală, mecanisme, evaluare*

INTRODUCTION

The arterial pressure may vary between large limits. If the perfusion pressure of the brain varies, the flow at this level varies very little. This phenomenon is known as the autoregulation of the cerebral circulation (1, 6, 7).

The autoregulation of the cerebral circulation is the mechanism by which the blood flow is maintained constant between large limits of the arterial pressure.

Autoregulation occurs only between certain pressure limits. Thus, the blood flow varies little between these limits and the clinical effects are minimal. If the pressure decreases or increases very much, the process of autoregulation is exceeded and the perfusion pressure is compromised. In decreased pressure, the blood flow also decreases, while in increased pressures, the blood flow increases very much, too. These mechanisms are encountered in human physiology and represent active processes through which the brain reacts to different pressure variations. When this process is compromised, the lack of perfusion occurs, as well as its excessive increase. These are mechanisms involved in the physiopathology of the ischemic, cerebral vascular accident or respectively hemorrhagic CVA (3, 4, 13, 24, 25, 30, 31, 32).

The smaller value is defined as the value of the mean arterial pressure under which CBF decreases under the border, while the larger value represents the value of the mean arterial pressure over which CFB increases over the border (60 and respectively 150 mmHg) (15, 26).

The mechanisms of the blood flow autoregulation.

The specialized literature present 2 possible mechanisms for autoregulation: myogenic reaction and metabolic regulation. The stimulation of the sympathetic nervous system and the antagonism of the renin-angiotensin system modulate the blood flow autoregulation, changing the entire curve towards higher or smaller values of the arterial pressure (26).

Cerebral autoregulation is depended on the intracranial pressure, venous cerebral pressure (23, 28, 29, 30). The data gathered until now involve both the animals and the humans. Thus, Muhonen and his collaborators (21) examined the arterial pressure, the regional cerebral blood flow and the mean carotid artery in a batch of 10 dogs. Regarding this experimental occlusion pattern of internal carotid artery, Muhonen and his collaborators (21) studied the cerebral haemorrhage effect on the cerebral circulation. This reduced the mean arterial pressure with 50 up to 25 mmHg. The cerebral blood flow decreased from 87 +/- 5 to 6 +/- 1 ml/100 g per minute.

Due to the fact that the autoregulation process cannot be emphasized directly, there were studies for shaping the autoregulation mechanisms (9). Giulioni and Ursino (9) studied the implications of the changes of the perfusion pressure on the cerebral autoregulation hemodynamics and intracranial pressure. The authors

used a mathematical method of the intracranial hemodynamics and of the cerebrospinal fluid dynamics. This interaction exists, but the specialized literature has no data thereof. In the case of the normal intracranial dynamics, the decrease of the systemic arterial pressure from 100 to 60 mmHg led to a slight decrease of the cerebral perfusion pressure. On the other hand, in case of a brutal obstruction and a severe alteration of the intracranial dynamics, a slight decrease of the systolic arterial pressure with 10 mmHg brought about a brutal increase of the intracranial pressure. The authors studied the case of a correct autoregulation, in the case in which the pressure-volume index was positively correlated to the mean arterial pressure. At the same time, when the inferior value of the autoregulation was exceeded, a negative correlation to the mean arterial pressure was obtained. However, the autoregulation curve was not described in detail, through a general formula. Gao and the collaborators (5) reviewed the main patterns of the autoregulation and issued an empiric pattern based on the principles of hemodynamics and on the existing experimental data. The authors inserted a simplification in their own pattern, that is the cerebral venous pressure and the intra-cerebral pressure was considered zero. Thus, the changes in the perfusion pressure were induced by the changes in the systemic arterial pressure.

The authors reviewed the main autoregulation patterns existing in literature. The authors' effort was based on finding a formula which should generate both the superior and the inferior limit of the autoregulation.

Hemodilution leads to the increase of the cerebral blood flow through compensatory vasodilatation and not through the decrease of the blood viscosity (34).

Gao and his collaborators (5) defined the following three types of autoregulation curves, based on the literature data:

1. Type 1 (with fixed and variable vascular reactivity) – this is the simplest pattern and is based on the hypothesis that reaching the inferior, respectively the superior limits of the autoregulation is made only after vasodilatation, respectively after vasoconstriction of the vascular resistance bed.
2. Type 2 is similar to type 1, with the exception of the flow-pressure relation above the superior limit of the autoregulation, which has the same behaviour as that placed below the inferior limit of the autoregulation. These two lines are parallel. The summarised data of the multiple experimental studies represented the basis for the scientific proof of this type 2 of the cerebral blood flow autoregulation.
3. Type 3 represents the direct approximation of the autoregulation curve observed in order to get a mathematical curve which should describe the autoregulation. These curves may be approximated through a polynomial curve of stage 3.

The autoregulatory curve is changed towards large pressures in chronic hypertension. Thus, the tolerance to acute decreases of arterial pressure is affected. Simultaneously, brain tolerance to acute increases of arterial pressure is improved. This change in the autoregulation limits is due to the structural and functional (hemodynamics) changes within the cerebral resistance vessels. These adaptive changes are partially reversible after the chronic treatment with antihypertensive agents.

The first observations on the cerebral autoregulation were made by Fog (quoted by Strandgaard and Paulson (32) 60 years ago, when he was studying the pialis vessels of the cat through a cranial window. Fog concluded that the autoregulatory vasomotor reactions are independent of the neurogenic stimuli. This observation is still valid, with minor changes.

Spencer curve is a polynomial curve of stage 3, which predicts the speed of the cerebral blood flow. This has a linear component and is based on Hagen-Poiseuille' law, on the continuity principle and on the cerebrovascular resistance. The theoretic pattern gives relations between the flow speed, the volume of the flow and the reduced size of the residual vascular lumen.

Blood flow autoregulation is defined as the mechanism through which the flow of an organ or vascular bed is kept almost constant, despite of the changes of the cerebral pressure. Regarding the reconsideration based on the cerebral blood flow (CBF), Lassen (16) established the concept of cerebral autoregulation based on the constancy of the blood flow during the changes of the pressure and the existence of a smaller level of the CBF was also proved.

Heistad and Kontos (10) define the cerebral blood flow autoregulation as the occurrence of the vasodilatation, when the cerebral pressure decreases and as the occurrence of the vasoconstriction, when the pressure increases. This definition emphasises the vasomotor function of the resistance vessels. We believe that the definition of the cerebral blood flow autoregulation, the way it was proposed in other interpretations (14) is also adequate for the cerebral blood flow evaluation, as long as it may be assessed through different methods. The other proposed method could be more precise, but its value is applied to the experiments in vitro and on animals, by measuring the activity of the vascular muscles (14).

The limits of the autoregulation of the cerebral blood flow.

The superior, respectively the inferior limits are fixed and vary both in physiological and pathological conditions.

The activation of the sympathetic nerves results in the positive modification, both of the inferior limit and of the superior one. These changes may be interpreted as a protective reaction, because the acute increases of the arterial pressure are usually accompanied by sympathetic activation, as Markus and Cullinane have proved (18).

CBF autoregulation is efficient for different perfusion pressures. In normotension, it was estimated that these limits are at the level of the mean arterial pressure of 60 and respectively 150 mmHg, under the smaller limit. Still, the resistance vessels are not dilated at

maximum, because dilatation may be induced with hypercapnia or medication. The oxygen consumption of the brain may be maintained by increasing the oxygen extraction from the blood. If, subsequently, the arterial pressure is reduced, even this mechanism becomes inadequate and the results of the network will show a decrease of the cerebral metabolic oxygen rate (22).

Above the larger limit, vasoconstriction leads to an increase of the intraluminal pressure and of the CBF. The increased intraluminal pressure brings about a strong dilatation of the arterioles' segment, with vibrations in the calibres of the vessels and dysfunctions of the blood barriers (22, 32). As a consequence, secondary decreases of the flow may occur, due to the cerebral edema.

There are static and dynamic methods for the study of the cerebral autoregulation. The cerebral blood flow or the speed of the cerebral blood flow is measured during the important modifications of the blood pressure that are usually induced pharmacologically. These techniques could not be performed in many patients due to the high risk of cerebral vascular accident, as a result of the modifications of the blood pressure that may lead to cerebral ischemia (27). As a result, the majority of the authors used indirect measurements of the cerebral autoregulation, such as the vasodilatator response to hypercapnia, the way Panerai and his collaborators have mentioned (27).

White and Markus (35) studied the dynamic cerebral autoregulation in the patients with carotid stenosis. The authors used the method described by Newell and his collaborators (23) in order to establish the dynamic cerebral autoregulation, by using ultrasonography. The idea of this method was to improve the reactivity method to CO_2 and acetazolamid. These two methods were proved to be correlated to the patients with stenosis and internal carotid occlusions. The limits of these methods are related to respiration, which increases the level of CO_2 and as a result, it increases the arterial pressure (33). This may lead to increases of the cerebral blood flow, which is due to the passive autoregulation. As a result, this technique may underestimate the degree of affection of the cerebral hemodynamics. On the other hand, CO_2 is not necessary a physiologic response.

Physiological modulation. The activation of the alfa-adrenergic sympathetic nerves changes the limits of the autoregulation towards higher pressures and the acute derivation changes the autoregulations limits towards lower pressures (17). Chronic sympathetic denervation does not change the autoregulation limits. The sympathetic nervous system acts predominantly on the larger cerebral resistance vessels, while autoregulation is predominantly on the smaller resistance vessels.

Renin – angiotensin system – also affects the CBF autoregulation. The descendent modification of the higher limit is attenuated by the simultaneous stimulation of the superior cervical ganglion in rats, which prove an interaction between the renin-angiotensin system and the sympathetic nervous system (3, 4). The myogenic hypothesis proves that the smooth muscles of the resistance arteries directly respond to the alterations of the perfusion pressure by contraction, during the increase of the pressure and by relaxation, during the pressure reduction.

The responses in the cerebral resistance arteries are obtained through this mechanism that may occur few seconds after the mechanism has launched them. There are experimental data that prove a certain constriction at the level of arteries, as a response to the intravascular pressure. (19).

The cerebral blood flow in chronic arterial hypertension.

Chronic arterial hypertension produces both changes in the functional and structural hemodynamics of the cerebral resistance vessels. These adaptable changes are partially reversible after the chronic treatment with hypertensive agents. The understanding of the functional level of adaptation or inadaptation is important for treatment assessment in each patient. The treatment of the arterial hypertension is important for preventing the stoke, whose risk is closely related to hypertension.

During the long term treatment, a number of hypertensive patients readapt the cerebral blood flow autoregulation almost to the normal limit. Last but not least, in case a sudden decrease of the arterial hypertension takes place, exceeding the inferior limit of the autoregulation, the brain may react through the increase of the oxygen extraction from the blood, the way Strandgaard and Paulson have proven (32).

The cerebral blood flow autoregulation in uncomplicated arterial hypertension, but in the smaller and larger limits are changed into high values of the arterial pressure. As a consequence of the structural changes in the cerebral arteries, the capacity of the resistance vessels for the maximal vasodilatation is reduced (8, 11).

Morphological changes in the cerebral arteries.

The degenerative structural and adaptation changes from the small resistance vessels represent the main factor responsible for the increase of the cerebrovascular resistance. The concept of the enlarged cerebrovascular resistance of the chronic hypertension in comparison with the normotension occurred as a result of the fundamental observation that the cerebral blood flow is constant, being the same in normotensive people and in hypertensives. As long as the mean arterial pressure which stagnates is larger, the vascular resistance should be larger. In muscular arteries, the mean is increased and fibrous, with the degeneration of the smooth muscular cells and with the thickness of the intimal layer. At brain level, these changes may be associated to the formation of the microaneurisms, whose rupture may represent a major cerebral haemorrhage (5, 8, 15, 22, 27).

Assessment of the cerebral autoregulation in humans.

There are two types of autoregulation assessment – static and dynamic. The values of the stationary flux are determined by taking into account an interval of arterial pressures. This type of assessment may be performed

through the use of drugs or changes in the blood volume. In order to establish the complete limit of autoregulation, it is necessary that the blood pressure should vary within this interval. One of the limits of this method is the existence of a free interval between establishment and assessment.

The dynamic autoregulation is made through the dynamic method. By the help of the transcranial Doppler ultrasonography, the assessment of the cerebral blood flow and of the blood speed may be accomplished. (19, 20). The cerebral autoregulation in carotid stenosis, ischemic cerebral vascular accidents (35) and cranial-cerebral traumatisms was assessed through this method (12).

Treatment effect on the cerebral blood flow.

The adaptation or the change to the right of the CBF autoregulation curve, which affects the tolerance to acute hypotension could be reversible with antihypertensive treatment on long term (28). Regarding a study related to the CBF autoregulation in hypertensive patients, it was proved that the smaller limit of the autoregulation recorded smaller values (still, not as small as in normotensive patients) in a group of patients who had severe hypertension and who have treated it well, as against those with untreated severe hypertension. Probably, in the hypertensive patients with reversible structural changes (generally, muscular hypertrophy) of the cerebral arteries, a relative complete adaptation of the CBF autoregulation curve takes places after the treatment. The research on the peripheral circulation shows that only 2 or 3 weeks are necessary for a structural vascular readaptation (29). There are other studies that show that the functional signs of the morphological changes are, to a certain extent, persistent (28). It is not known whether the readaptation process is facilitated by certain antihypertensive drugs, more than the others.

BIBLIOGRAPHY

1. Aaslid R, Newell, DW, Stooss R, et al. Assessment of Cerebral Autoregulation Dynamics from Simultaneous Arterial and Venous Transcranial Doppler Recordings in Humans. Stroke 1991; 22:1148-1154.
2. Alexandrov AV. The Spencer's Curve: Clinical Implications of a Classic Hemodynamic Model. J Neuroimaging 2007; 17:6-10.
3. Baumel JJ, Gerchman L. The Avian Intercarotid Anastomosis and its Homologue in Other Vertebrates. Am J Anat 1968; 122:1-18.
4. Busija DW, Heistad DD, Marcus ML. Continuous Measurements of Cerebral Blood Flow in Anesthetized Cats and Dogs. Am J., Physiol 1981; 241:228-233.
5. Gao E, Young WL, Pile-Spellman J, et al. Mathematical Considerations for Modelling Cerebral Blood Flow Autoregulation to Systemic Arterial Pressure. Am J Physiol 1998; 274:H1023-H1031.
6. Geraud J, Bes A, Rascol A, et al. Les measures du debit sanguine cerebral dans les stenoses e les thrombose de la carotide interne: etude critique de leurs possibilities. Rev Neurol 1966; 115:695-702.
7. Gibbs JM, Wise RJS, Leenders KL, et al. Evaluation of Cerebral Perfusion Reserve in Patients with Carotid Artery Occlusion. Lancet 1984; 8372:310-314.
8. Gur AY, Bova I, Bornstein NM. Is Impaired Cerebral Vasomotor Reactivity a Predictive Factor of Stroke in Asymptomatic Patients? Stroke 1996; 27:2188-2190.
9. Giulioni M, Ursino M. Impact of Cerebral Perfusion Pressure and Autoregulation on Intracranial Dynamics: a Modelling Study. Neurosurgery1996; 39:1005-1014.
10. Heistad DD, Kontos HA. Cerebral Circulation. In: Stheperd JT, Abbourd FM, (Eds.) Handbook of Physiology Society, Lippincott, Bethesda, 1983:137-182.
11. Hageendal E, Johanson B. Effects of Arterial Carbon Dioxide Tension and Oxygen Saturation on Cerebral Blood Flow Autoregulation in Dogs. Acta Physiol Scand 1965; 66 (suppl.):27-53.
12. Hlatky R, Furuya Y, Valadka AB. Dynamic Autoregulatory Response after Severe Head Injury. J Neurosurg 2002; 97:1054–1061.
13. Iida N. Different Flow Regulation Mechanisms Between Celiac and Mesenteric Vascular Beds in Conscious Rats, Hypertension 1995; 25:260-265.
14. Kontos HA. Validity of Cerebral Arterial Blood Flow Calculations from Velocity Measurements. Stroke 1989; 20:1-3.
15. Lassen NA, Christensen MS. Physiology of Cerebral Blood Flow. Br J Anaesth 1976; 48:719-734.
16. Lassen NA. Cerebral Blood Flow and Oxygen Consumption in Man. Physiol Rev 1959; 39:183-238.
17. Lindegaard KF, Lundar T, Wiberg J, et al. Variations in Middle Cerebral Artery Blood Flow Investigated with Noninvasive Transcranial Velocity Measurements. Stroke 1987; 18:1025-1030.
18. Markus H, Cullinane M. Severely Impaired Cerebrovascular Reactivity Predicts Stroke and TIA Risk in Patients with Carotid Artery Stenosis and Occlusion. Brain 2001; 124:457-467.
19. Markus HS, Molloy J. Use of a Decibel Threshold in Detecting Doppler Embolic Signals. Stroke 1997; 28:692-695.
20. Markus HS. Transcranial Doppler Ultrasound, J Neurol Neurosurg Psychiatry 1999; 67:135-137.
21. Muhonen MG, Sawin PD, Loftus CM, et al. Pressure-Flow Relations in Canine Collateral-Dependent Cerebrum. Stroke 1992; 23:988-94.
22. McHerry JLC, West JW, Cooper ES, et al Cerebral Autoregulation in Man. Stroke 1974; 5:695-705.
23. Newell DW, Aaslid R, Lam A, et al. Comparison

of Flow and Velocity during Dynamic Autoregulation Testing in Humans. Stroke 1994; 25:793-797.
24. Paulson OB. Cerebral Apoplexy (stroke): Pathogenesis, Pathophysiology and Therapy as Illustrated by Regional Blood Flow Measurements in the Brain. Stroke 1971; 2:327-360.
25. Pascu I, Rădoiu D, Pop A. A Computerized Model of the Circle of Willis, Rev Med 1988; 34:107-113.
26. Paulson OB, Lassen NA, Skinhoj E. Regional Cerebral Blood Flow in Apoplexy Without Arterial Occlusion. Neurology 1970; 20:125-138.
27. Panerai RB, White RP, Markus HS, et al. Grading of Cerebral Dynamic Autoregulation from Spontaneous Fluctuations in Arterial Blood Pressure. Stroke 1998; 29:2341-2346.
28. Paulson OB, Waldemar G, Schmidt JF, et al. Cerebral Circulation under Normal and Pathological Conditions. Am J Cardiol 1989; 63:2C-5C.
29. Rados W, duBoulay GH. Paradoxical Dilation of Large Cerebral Arteries in Hypocapnia in Man Stroke 1976; 7:569-572.
30. Siebler M, Sitzer M, Steinmetz H. Detection of Intracranial Emboli in Patients with Symptomatic Extracranial Carotid Artery Disease Stroke 1992; 23:1652-1654.
31. Stoica E, Meyer JS, Kawamura Y, et al. Central Neurogenic Control of Cerebral Circulation. Effects of Intravertebral Injection of Pyrithioxin on Cerebral Blood Flow and Metabolism. Neurology 1973; 23:687-698.
32. Strandgaard S, Paulson OB. Cerebral Autoregulation. Stroke 1984; 15:413-416.
33. Smielewski P, Czosnyka M, Pickard JD, et al. Clinical Evaluation of Near-Infrared Spectroscopy for Testing Cerebrovascular Reactivity in Patients with Carotid Artery Disease. Stroke 1997; 28:331-338.
34. Von Kummer R, Scharf J, Back T, et al. Autoregulatory Capacity and the Effect of Isovolemic Hemodilution on Local Cerebral Blood Flow. Stroke 1988; 19:594-597.
35. White RP, Markus HS. Non-Invasive Determination of Impaired Dynamic Cerebral Autoregulation in Carotid Artery Stenosis. Stroke 1997; 28:1340–1344.